Original Research

Deliveries Among Patients With Maternal Hepatitis C Virus Infection in the United States, 2000–2019

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OBJECTIVE: To assess clinical characteristics, trends, and outcomes associated with the diagnosis of hepatitis C virus (HCV) infection during pregnancy.

METHODS: This cross-sectional study analyzed delivery hospitalizations using the National Inpatient Sample. Temporal trends in both diagnosis of HCV infection and clinical characteristics associated with HCV infection were analyzed using joinpoint regression to estimate the average annual percent change (AAPC) with 95% CIs. Survey-adjusted logistic regression models were fit to assess the association among HCV infection and preterm delivery, cesarean delivery, and severe maternal morbidity (SMM), adjusting for clinical, medical, and hospital factors with adjusted odds ratios (aORs) as the measure of association.

RESULTS: An estimated 76.7 million delivery hospitalizations were included, in which 182,904 (0.24%) delivering individuals had a diagnosis of HCV infection. The prevalence of HCV infection diagnosed in pregnancy increased nearly 10-fold over the study period, from 0.05% in 2000 to 0.49% in 2019, representing an AAPC of 12.5% (95% CI 10.4–14.8%). The prevalence of clinical characteristics associated with HCV infection also increased over the study period, including opioid use disorder (from 10 cases/10,000 birth hospitalizations to 71 cases/10,000 birth hospitalizations), nonopioid substance use disorder (from 71 cases/10,000 birth hospitalizations to 217 cases/10,000 birth hospitalizations), mental health conditions (from 219 cases/10,000 birth hospitalizations to 1,117 cases/10,000), and tobacco use (from 61 cases/10,000 birth hospitalizations to 842 cases/10,000). The rate of deliveries among patients with two or more clinical characteristics associated with HCV infection increased from 26 cases per 10,000 birth hospitalizations to 377 cases per 10,000 delivery hospitalizations (AAPC 13.4%, 95% CI 12.1–14.8%). In adjusted analyses, HCV infection was associated with increased risk for SMM (aOR 1.78, 95% CI 1.61–1.96), preterm birth (aOR 1.88, 95% CI 1.8–1.95), and cesarean delivery (aOR 1.27, 95% CI 1.23–1.31).

CONCLUSION: Diagnosis of HCV infection is increasingly common in the obstetric population, which may reflect an increase in screening or a true increase in prevalence. The increase in HCV infection diagnoses occurred in the setting of many baseline clinical characteristics that are associated with HCV infection becoming more common.

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Hepatitis C virus (HCV) infection is becoming increasingly prevalent in pregnancy. An analysis of U.S. natality data found that the prevalence of maternal HCV infection increased 161% from 2009 to 2017.[1] In 2019, more than 60% of acute HCV infection cases reported to the Centers for Disease Control and Prevention were among patients aged 20–39 years.[2] Given this increasing prevalence among patients of reproductive age, the CDC recommended

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Given that this study involved a de-identified and publicly available data set, the IRB review by both Columbia University and the University of California, San Francisco, deemed this exempt from review.

Each author has confirmed compliance with the journal's requirements for authorship.

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universal screening for HCV infection in 2020, which was formally endorsed by the American College of Obstetricians and Gynecologists in 2021.[3]

The opioid epidemic and resultant increasing rates of intravenous drug use are thought to account for a large proportion of the rising incidence of HCV infection. However, 50% of individuals with HCV infection report no history of intravenous drug use.[4] As such, there is a knowledge gap with regards to other risk factors, demographic and clinical characteristics, and comorbidities associated with HCV infection among pregnant patients.

Similarly, there is a knowledge gap with regards to obstetric outcomes among patients with HCV infection. The existing literature shows mixed results, with some studies demonstrating an association between HCV infection and poor obstetric outcomes and others supporting no such risks.[5–10] Additionally, there is a paucity of literature with regards to the association of HCV infection with severe maternal morbidity (SMM). In this study, our objectives were to 1) evaluate temporal trends in the diagnosis of HCV infection in pregnancy and clinical characteristics previously associated with HCV infection over a 20-year period (2000–2019) and 2) analyze maternal outcomes at delivery hospitalization among patients with a diagnosis of HCV infection.

METHODS

We identified delivery hospitalizations among patients with a diagnosis of HCV infection using the National Inpatient Sample (NIS) created by the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project from 2000 to 2019 using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. The NIS comprises approximately 20% of all hospitalizations nationally and is one of the largest publicly available, all-payer inpatient databases in the United States.[11] From 2000 to 2011, the NIS included all hospitalizations from a sample of individual hospitals. In 2012 and thereafter, the NIS involved a systematic sampling design with proportionate representation of individual hospitals, with 20% of discharge records from all participating hospitals included.[12–14] Population weights can be applied to the NIS to create national estimates; these weights were applied for this study.[15] Although weights may inappropriately narrow CIs due to the large sample size in the NIS, CI estimates with and without weighting are generally similar. On October 1, 2015, NIS coding transitioned from ICD-9-CM to ICD-10-CM coding. To perform analyses across the study period and coding change, ICD-9-CM codes were translated to ICD-10-CM codes using the publicly available General Equivalence Mappings provided by the Centers for Medicare & Medicaid Services and the National Center for Health Statistics.[16] Given that this study involved a de-identified and publicly available data set, the university IRBs deemed this study exempt from review.

The current analysis was restricted to delivery hospitalizations among women of reproductive age, between 15 and 54 years. Because of the de-identified nature of the NIS and the lack of linkages, the unit of measure of this study was the delivery hospitalization, with the limitation that multiple pregnancies are unable to be accounted for. Hospitalizations among patients with HCV infection were identified using ICD-9-CM and ICD-10-CM diagnosis codes. We identified demographic, obstetric, and hospital covariates in the NIS and by using diagnosis codes, and compared them based on the presence or absence of HCV infection.[17,18] Demographic factors included year of delivery, maternal age, self-reported maternal race and ethnicity, insurance status (Medicaid, private, Medicare, other, uninsured), and median income quartile based on ZIP code. Self-reported maternal race and ethnicity were included in this analysis given that there are significant associations with our outcomes of interest. Hospital characteristics included location and teaching status (urban teaching, urban nonteaching, and rural) and geographic region (Northeast, Midwest, South, or West). Comorbid medical conditions were identified using diagnosis codes and included asthma, obesity, chronic hypertension, pregestational diabetes, systemic lupus erythematosus, and gestational diabetes. Obstetric diagnoses included prior cesarean delivery and multiple gestation.

This study had three primary objectives. The first objective was to determine temporal trends in the prevalence of HCV infection diagnosis at delivery hospitalization. The proportion of deliveries by year among patients with a diagnosis of HCV infection was identified and trends analysis during the study time (2000–2019) were conducted using the National Cancer Institute's Joinpoint Regression 4.8.0.1. This program employs linear segmented regression and logarithmic transformation to determine the average annual percent change (AAPC).[19,20] The program also estimates the average annual percentage change over the whole study period.[21]

The second objective was to analyze trends in clinical characteristics and risk factors associated with HCV infection diagnosis (denoted in this study as clinical factors) among patients at delivery hospitalization. Clinical factors analyzed include substance use

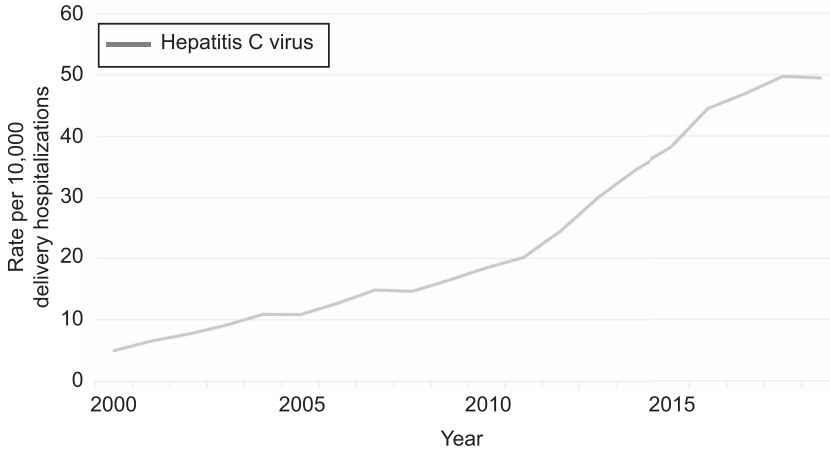

Fig. 1. Trends in hepatitis C diagnoses among patients with delivery hospitalizations.

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disorder (exclusive of opioids), opioid use disorder (OUD), sexually transmitted infection (exclusive of HCV infection), smoking, and mental health condition diagnoses.[22–25] The number of clinical factors associated with HCV infection was categorized as zero, one, or two or more for each patient. Trends in clinical factors were analyzed using the joinpoint regression program. Univariable survey-adjusted logistic regression models were performed to assess associations between clinical factors and the likelihood of a delivery hospitalization among patients with HCV infection. As a sensitivity analysis, trends in risk factors for perinatal transmission of HCV–human immunodeficiency virus (HIV) co-infection and OUD–were analyzed.[26–28] Hepatitis C viremia could not be evaluated due to the inherent limitations in administrative data coding. We conducted joinpoint regression analyses to assess these trends.

The third objective was to analyze maternal outcomes during delivery hospitalizations among patients with and without HCV infection. Obstetric outcomes included hypertensive disorders of pregnancy, cesarean delivery, preterm delivery, and non–transfusion-related SMM at delivery hospitalization. Non–transfusion-related SMM was defined using criteria from the CDC, which is a composite of 25 diagnoses, conditions, and procedures associated with adverse maternal outcomes excluding transfusion.[29] We fit univariable and multivariable survey-adjusted logistic regression models to assess the association between HCV infection diagnosis and adverse outcomes. Models were then adjusted for the previously mentioned demographic, clinical, and obstetric covariates. We calculated unadjusted odds ratios (ORs) and adjusted odds ratios with 95% CIs as measures of association.

Demographic and clinical factors were compared between groups by analyzing the absolute standardized mean difference (SMD) with a value greater than 0.1 (10%) interpreted as a meaningful magnitude of

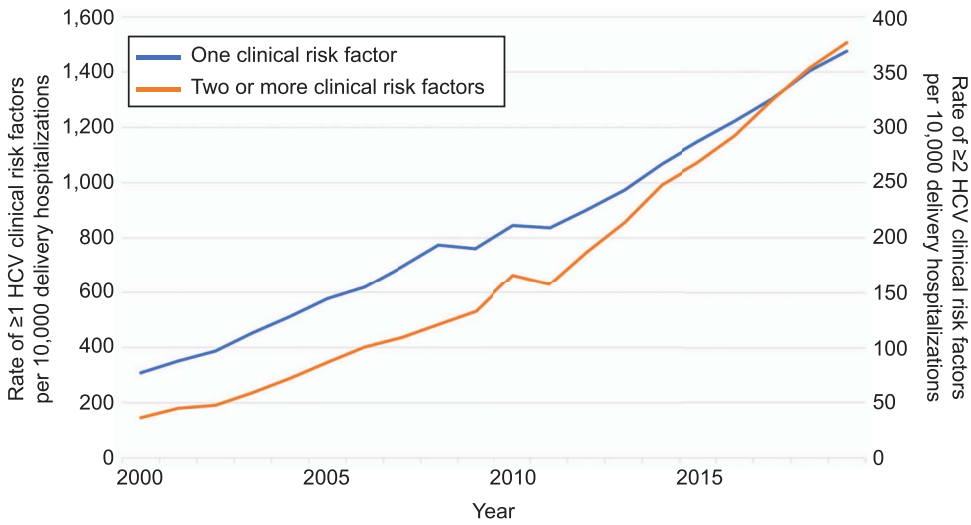

Fig. 2. Trends in clinical risk factors for hepatitis C infection (HCV) among patients with delivery hospitalizations. Clinical risk factors include substance use (exclusive of opioids), opioid use, sexually transmitted infection (exclusive of HCV infection), smoking, and mental health condition diagnoses.

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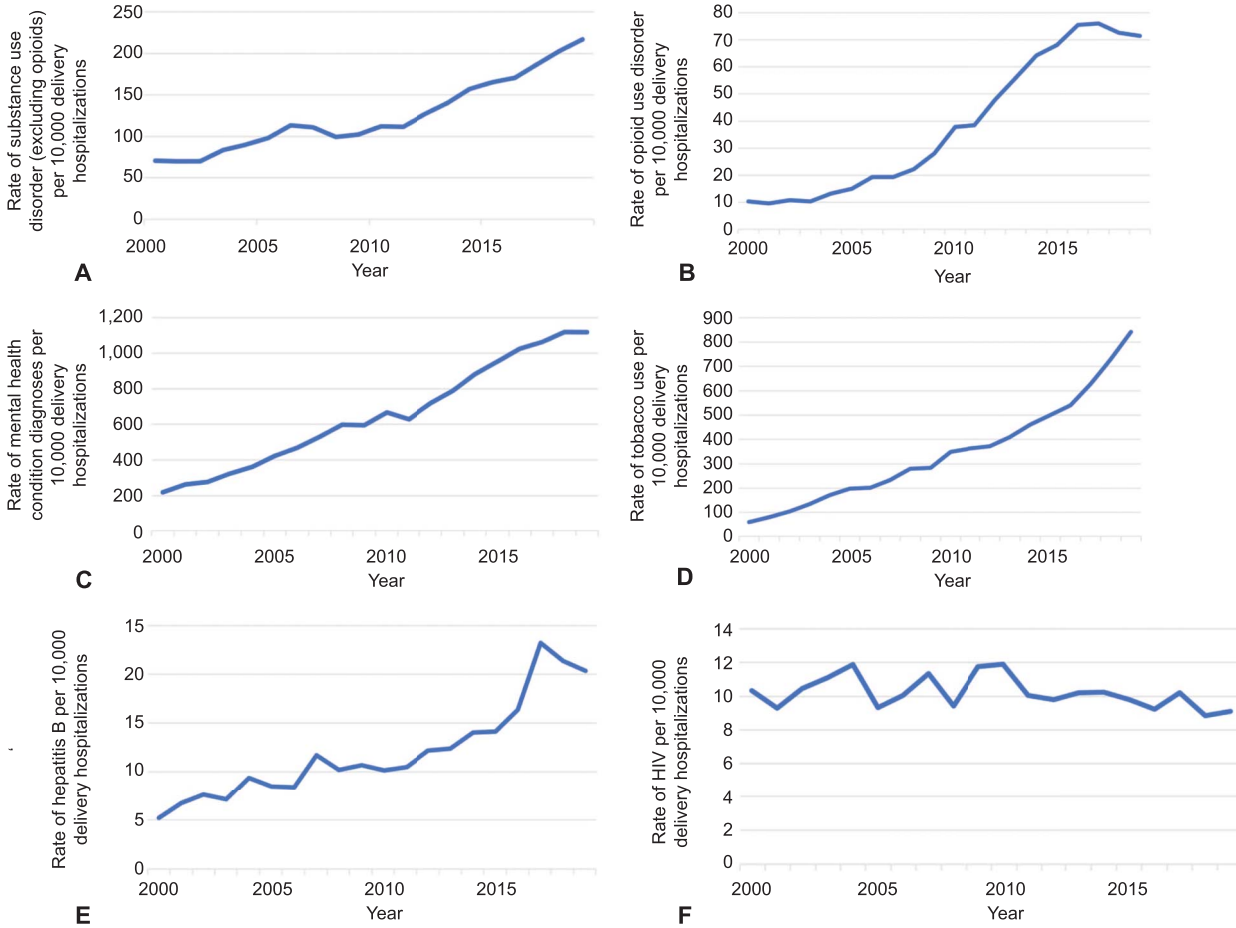

Fig. 3. Trends in risk factors for hepatitis C infection among patients with delivery hospitalizations. **A**. Substance use disorder excluding opioids (average annual percent change [AAPC] 6.2%, 95% CI 3.9–8.5). **B**. Opioid use disorder (AAPC 10.9%, 95% CI 7.3–14.6). **C**. Mental health condition diagnoses (AAPC 8.9%, 95% CI 7.9–9.9). **D**. Tobacco use (AAPC 14.7%, 95% CI 12.9–16.6). **E**. Hepatitis B (AAPC 6.8%, 95% CI 5.6–8.0). **F**. Human immunodeficiency virus (HIV) (AAPC −0.7%, 95% CI −1.4 to 0.0).

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difference between the two groups.[30] Analyses were repeated with unweighted data as a supplemental analysis. All analyses were performed with SAS 9.4, with the exception of the temporal trends analysis performed with the joinpoint regression program. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies for this analysis.[31] Given that the data were de-identified, the study was deemed exempt by the Columbia University institutional review board.

RESULTS

From 2000 to 2019, an estimated 76,698,773 delivery hospitalizations were identified, in which 182,094 (0.24%) delivering individuals had a diagnosis of HCV infection. Unweighted, the analysis included 15,893,692 delivery hospitalizations, including 37,129 (0.23%) patients with HCV infection (Appendix 1, available online at http://links.lww.com/AOG/D70). During the study period, the presence of a diagnosis of HCV infection during delivery hospitalization increased from 50 cases per 100,000 delivery hospitalizations to 494 cases per 100,000 delivery hospitalizations (AAPC 12.5%, 95% CI 10.4–14.8%) (Fig. 1).

The proportion of deliveries among patients with at least one HCV infection clinical factor increased from 308 cases per 10,000 delivery hospitalizations to 1,476 cases per 10,000 delivery hospitalizations from 2000 to 2019 (AAPC 8.6%, 95% CI 7.8–9.4%) and the proportion of deliveries among patients with two or

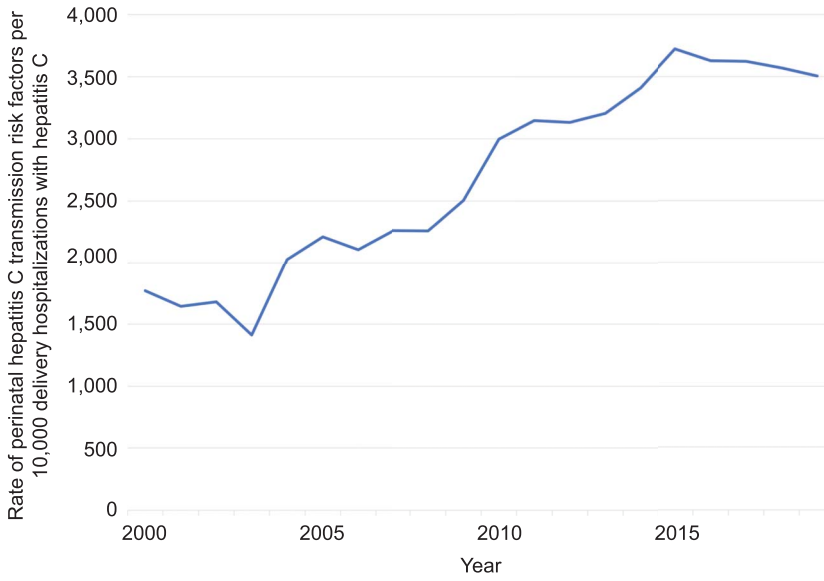

Fig. 4. Trends in perinatal hepatitis C transmission risk factors among patients with delivery hospitalizations. Perinatal hepatitis C transmission risk factors included human immunodeficiency virus (HIV) co-infection, opioid use disorder, or both.

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more clinical factors associated with HCV infection increased from 26 cases per 10,000 delivery hospitalizations to 377 cases per 10,000 delivery hospitalizations (AAPC 13.4%, 95% CI 12.1–14.8%) (Fig. 2). Individual clinical factors associated with HCV infection, including tobacco use (61–842 cases/10,000 delivery hospitalizations; AAPC 14.7%, 95% CI 12.9–16.6%), OUD (10–71 cases/10,000 delivery hospitalizations, AAPC 10.9%, 95% CI 7.3–14.6%), mental health conditions (219–1,117 cases/10,000 delivery hospitalizations, AAPC 8.9%, 95% CI 7.9–9.9%), and nonopioid substance use disorders (71–217 cases/10,000 delivery hospitalizations, AAPC 6.2%, 95% CI 3.9–8.5%) had the largest increases from 2000 to 2019 (Fig. 3). The proportion of deliveries among patients with HCV infection with transmission risk factors (HIV co-infection and OUD) increased from 1,766 cases per 10,000 delivery hospitalizations to 3,505 per 10,000 delivery hospitalizations from 2000 to 2019 (AAPC 4.5%, 95% CI 3.6–5.4%) (Fig. 4). In sensitivity analyses of unweighted data, the rate of patients with at least one clinical factor associated with HCV infection increased from 308 cases per 10,000 delivery hospitalizations to 1,475 cases per 10,000 delivery hospitalizations (AAPC 8.6%, 95% CI 7.8–9.4%); the rate of patients with two or more clinical factors associated with HCV infection increased faster, from 36 cases per 10,000 delivery hospitalizations to 377 cases per 10,000 delivery hospitalizations (AAPC 13.4%, 95% CI 12.1–14.8%) (Appendix 2, available online at http://links.lww.com/AOG/D70).

Patients with HCV infection were more likely to have HIV infection (1.3% vs 0.1%, SMD 14%) and hepatitis B infection (1.6% vs 0.1%, SMD 16%). They were also more likely to smoke tobacco (48.1% vs 6.1%, SMD 110%), have a mental health condition (20.2% vs 3.1%, SMD 56%), or an OUD diagnosis (44.2% vs 1.4%, SMD 91%) (Table 1; see Appendix 3, available online at http://links.lww.com/AOG/D70, for unweighted comparisons). Patients with an HCV infection diagnosis were also more likely to be non-Hispanic White individuals (71.8% vs 44.3%, SMD 60%), have Medicaid insurance (76.8% vs 41.2%, SMD 87%), asthma (8.0% vs 3.2%, SMD 21%), and prior cesarean delivery (21.2% vs 15.8%, SMD 14%). In univariable analysis, diagnoses of OUD (OR 141. 19, 95% 134.47, 148.24), nonopioid substance use disorder (OR 56.22, 95% CI 53.61–58.96), and tobacco smoking (OR 14.53, 95% CI 13.97–15.11) had the largest magnitude of association with HCV infection (Table 2).

Delivery hospitalizations among patients with HCV infection were associated with increased likelihood of non–transfusion-related SMM (OR 2.10, 95% CI 1.92–2.29), preterm birth (OR 1.75, 95% CI 1.69–1.82), and cesarean delivery (OR 1.33, 95% CI 1.30–1.37) (Table 3; see Appendix 4, available online at http://links.lww.com/AOG/D70, for unweighted comparisons). These estimates were similar after adjustment for clinical, demographic, and hospital factors.

DISCUSSION

Diagnoses of HCV infection at delivery hospitalization rose almost 10-fold over the study period, from 0.05% in 2000 to 0.49% in 2019. Consistent with prior

Table 1. Characteristics of the Study Population

Risk Factor	HCV Infection Diagnosis		SMD
	Yes	No	
Clinical factors			
HIV co-infection	76,177 (0.1)	2,300 (1.3)	0.14
Hepatitis B co-infection	88,537 (0.1)	2,733 (1.5)	0.15
OUD	1,086,846 (1.4)	81,497 (44.8)	1.20
Nonopioid SUD	233,395 (0.3)	54,931 (30.2)	0.91
Smoking	4,851,701 (6.3)	90,296 (49.6)	1.10
Psychiatric diagnosis	2,580,889 (3.4)	38,248 (21.0)	0.56
Maternal race			
Hispanic	14,531,544 (19.0)	14,593 (8.0)	
Non-Hispanic Black	8,917,165 (11.7)	10,493 (5.8)	
Non-Hispanic White	33,854,983 (44.3)	130,731 (71.8)	0.60
None of the above	6,977,562 (9.1)	9,436 (5.2)	
Unknown	12,235,426 (16.0)	16,842 (9.3)	
Age category (y)			
15–19	6,523,138 (8.5)	4,253 (2.3)	0.33
20–24	17,702,628 (23.1)	38,478 (21.1)	
25–29	21,371,682 (27.9)	62,020 (34.1)	
30–34	19,267,284 (25.2)	48,707 (26.8)	
35–39	9,491,639 (12.4)	22,729 (12.5)	
40–54	2,160,308 (2.8)	5,907 (3.2)	
Payer status			
Medicare insurance	443,153 (0.6)	4,257 (2.3)	0.87
Medicaid insurance	31,527,108 (41.2)	139,773 (76.8)	
Private insurance	39,938,239 (52.2)	27,983 (15.4)	
Self-pay	2,336,134 (3.1)	4,660 (2.6)	
No charge	136,926 (0.2)	245 (0.1)	
Other	2,010,341 (2.6)	4,597 (2.5)	
Missing	124,779 (0.2)	580 (0.3)	
Median income quartile by ZIP code			
1	18,292,962 (23.9)	71,036 (39.0)	0.45
2	18,507,615 (24.2)	50,074 (27.5)	
3	18,667,829 (24.4)	35,150 (19.3)	
4	19,866,833 (26.0)	21,858 (12.0)	
Missing	1,181,440 (1.5)	3,976 (2.2)	
Clinical comorbidities			
Asthma	2,434,134 (3.2)	14,592 (8.0)	0.21
Obesity	3,351,058 (4.4)	10,309 (5.7)	0.06
Chronic hypertension	1,085,205 (1.4)	4,544 (2.5)	0.09
Pregestational diabetes	709,968 (0.9)	2,414 (1.3)	0.02
Gestational diabetes	4,506,171 (5.9)	9,534 (5.2)	0.02
Prior cesarean delivery	12,073,025 (15.8)	38,593 (21.2)	0.14
Multiple gestation	1,376,876 (1.8)	3,572 (2.0)	0.01
Hospital location			
Rural	8,442,557 (11.0)	27,440 (15.1)	0.34
Urban nonteaching	28,046,027 (36.7)	42,194 (23.2)	
Urban teaching	39,801,250 (52.0)	111,875 (61.4)	
Hospital region			
Northeast	12,403,834 (16.2)	36,720 (20.2)	0.23
Midwest	16,284,349 (21.3)	34,377 (18.9)	
South	29,001,938 (37.9)	80,699 (44.3)	
West	18,826,558 (24.6)	30,298 (16.6)	

SMD, standardized mean difference; HIV, human immunodeficiency virus; OUD, opioid use disorder; SUD, substance use disorder.
Data are n (%) unless otherwise specified.

studies, hospitalizations among patients with HCV infection were associated with specific demographic characteristics including public insurance, being of non-Hispanic White race, and lower ZIP code income quartile.[1,32,33] Hepatitis C virus infection was associated with increased risk for adverse outcomes

Table 2. Clinical Factors Associated With a Diagnosis of Hepatitis C Virus Infection

	Unadjusted Models	
Clinical Factors	OR	95% CI
HIV infection	12.84	11.36–14.52
Hepatitis B infection	13.16	11.81–14.66
Nonopioid SUD	56.22	53.61–58.96
OUD	141.19	134.47–148.24
Smoking	14.53	13.97–15.11
Psychiatric diagnosis	7.62	7.24–8.01
Advanced maternal age	1.04	1.00–1.08
Medicaid insurance	4.71	4.46–4.98

OR, odds ratio; HIV, human immunodeficiency virus; SUD, substance use disorder; OUD, opioid use disorder.

including non–transfusion-related SMM, preterm birth, and cesarean delivery, even after adjusting for demographic and clinical factors. Clinical factors associated with HCV infection diagnosis in prior studies also broadly increased over the study period, including tobacco use, OUD, mental health conditions, hepatitis B virus infection, and substance use disorder exclusive of opioids.

Rates of diagnosis of maternal HCV infection are rapidly rising in the United States, and our study suggests an even higher rate of diagnosis among pregnant people than other recent studies.[1] This rise in delivery hospitalizations among patients with a maternal HCV infection diagnosis could be attributed to an increase in screening for HCV infection or to the rise of clinical factors associated with HCV infection. Our study found that the proportion of patients with two or more clinical factors associated with HCV infection has increased at a higher rate than those with one clinical risk factor. Our study also noted an increase in perinatal HCV transmission risk factors, which is concerning for rising perinatal HCV infection risk in the population.

In response to these trends, the American College of Obstetricians and Gynecologists recently updated their recommendations to screen universally for HCV infection in pregnancy.[3] Although there is currently no HCV treatment approved for use during pregnancy, pregnancy itself is a distinctive time of regular engagement in medical care. Pregnancy presents a unique opportunity to engage high risk and vulnerable populations and connect them to future care. Recognizing that pregnancy may be the only time that certain patients have access to care, some small studies have analyzed use direct-acting antiviral agents for treatment of HCV infection in pregnant women. A recent, small phase I clinical trial demonstrated a 100% HCV infection cure rate among nine pregnant volunteers, with no perinatal adverse effects or perinatal transmission noted.[34] As our study also noted higher rates of perinatal HCV transmission risk factors, further study is warranted to develop novel therapeutics and prevent neonatal transmission.

Our study has several limitations to consider. First, there was no universal screening for HCV infection during the study time period. We found both an increasing incidence of HCV infection diagnoses and HCV infection risk factors; thus, it is difficult to assess whether increasing rates of HCV infection diagnosis were the result of improved risk-based screening or reflect a true increase in the incidence of disease. It is possible that increased testing in and of itself could have led to higher rates of diagnoses. However, inpatient and outpatient lab screening results are not available in this database, so this could not be evaluated. Because of the increased awareness surrounding the opioid epidemic over the study time period, it is possible that more patients

Table 3. Comparison of Adverse Outcomes for Patients With and Without a Diagnosis of Hepatitis C Virus Infection (Weighted)*

	HCV Infection Diagnosis		Unadjusted Model		Adjusted Model	
Adverse Outcome	Yes	No	OR	95% CI	aOR	95% CI
Non–transfusion-related SMM	525,531 (0.7)	2,598 (1.4)	2.10	1.92–2.29	1.83	1.67–2.00
Preterm birth	4,950,079 (6.5)	19,699 (10.8)	1.75	1.69–1.82	1.89	1.82–1.96
Cesarean delivery	23,638,014 (30.9)	67,955 (37.3)	1.33	1.30–1.37	1.26	1.22–1.30
HDP	6,016,056 (7.9)	16,450 (9.0)	1.16	1.12–1.21	1.01	0.97–1.05

HCV, hepatitis C virus infection; OR, odds ratio; aOR, adjusted odds ratio; SMM, severe maternal morbidity; HDP, hypertensive disorders of pregnancy.

Data are n (%) unless otherwise specified.

* The table demonstrates counts and estimates from weighted data. The adjusted models include all of the demographic (maternal race, age category, payer status, median income quartile by ZIP code), clinical (asthma, obesity, chronic hypertension, pregestational diabetes, gestational diabetes, prior cesarean delivery, multiple gestation), and hospital factors (location, region) in Table 1.

were being screened and tested and, thus, that part of the observed increase was the result of verification bias. It is also possible that because of the lack of universal screening, patients with HCV infection were not identified in our study and that the true prevalence of disease is higher. Additionally, we relied on administrative hospital discharge data, which may be subject to underascertainment, misclassification, and lack of granularity.[35] We also did not have laboratory data to validate the diagnoses or provide additional diagnostic details, including acute compared with chronic infection and viral load. Additionally, we were not able to control for HIV viral load, which is known to be positively associated with HCV viral load.[36–38] Furthermore, when logistic regression is used in cross-sectional design, the OR can overestimate the prevalence ratio. Given the cross-sectional nature of this study, associations with adverse outcomes in the setting of HCV infection diagnosis should not be presumed to be causal or a direct result of HCV infection; they could be due confounding or to health care professional decision making.

Strengths of this study include use of a large, nationally representative data set, which enabled meaningful statistical comparisons of relatively rare outcomes. Additionally, this analysis spanned 20 years, allowing for assessment of trends over time, and producing results generalizable to pregnant patients across the United States.

In summary, this study found that 1) the rate of diagnosis of maternal HCV infection among patients with delivery hospitalizations is increasing and remains significantly associated with adverse outcomes, 2) the prevalence of clinical factors associated with HCV infection has increased, and 3) perinatal HCV transmission risk factors are increasing. These findings support universal screening for HCV infection in pregnancy and that identifying and treating women at high risk for infection before pregnancy may be an important focus for optimizing care and mitigating perinatal HCV transmission.

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